REMARKS

Applicant respectfully requests reconsideration of the present application in view of the foregoing amendments and in view of the reasons that follow.

I. SUPPORT FOR CLAIM AMENDMENTS AND ADDITIONS

Claims 22, 30-31 and 33 are amended.

Claims 2 through 5, 7 and 8, and 11 through 20 were previously cancelled.

Claims 6, 9 and 10 were previously withdrawn as drawn to an non-elected invention.

In view of these amendments, Claims 1 and 21 through 46 are now pending in the application. No new matter has been added to the application by the proposed amendments. In particular, support for the claim limitations now present is found in the Specification as follows:

Claim Number	Amended Claim Limitation	Representative Examples of Specification Support
22	Non-chemotropic growth is stimulated in a region of the brain innervated by a targeted neuron.	Paragraph 0032; Example V (paragraphs 0082 through 0085).
30	Non-chemotropic growth is stimulated in a region of the brain innervated by a targeted neuron.	Paragraph 0032; Example V (paragraphs 0082 through 0085).
31	Non-chemotropic growth is stimulated in a region of the brain innervated by a targeted neuron.	Paragraph 0032; Example V (paragraphs 0082 through 0085).
33	Non-chemotropic growth is stimulated in a region of the brain innervated by a targeted neuron.	Paragraph 0032; Example V (paragraphs 0082 through 0085).

No new matter is introduced by these amendments. Entry thereof is therefore requested.

II. OVERVIEW OF THE INVENTION

The invention provides means for ameliorating the effects of the aging process on the brain. The invention further provides means for increasing growth or activity, including increases in axonal density, among neurons in a region of the brain than is innervated by the targeted neurons.

Previous reports (including the inventor's own previously issued patents) have indicated that localized neuronal atrophy can be modulated by treating the neuron with a growth factor. To this end, the growth factor is introduced into the neuron itself, or into the nearby brain tissue. Such growth is considered to be "chemotropic" in nature; i.e., where neurons respond directly, at the site of the treatment, to contact with a growth factor.

However, no previous report has suggested that treating one segment of a neuronal cell with growth factor can stimulate activity or growth in *another* part of the neuron. The invention provides means to stimulate such growth, even when the neuron extends a significant distance from the delivery site; e.g., a region of the brain having delivery sites therein that innervates, or is innervated by, another region of the brain. Such growth is "non-chemotropic" in nature; i.e., it likely occurs through triggering of a signaling pathway or other response in the neuron downstream of the site of contact between the neuron and the growth factor.

Therefore, practice of the invention to deliver a growth factor to the brain provides neuronal growth not only in the treated region of the brain (where a growth factor is delivered), but also in regions of the brain innervated by the treated neurons.

The present Office Action suggests that the invention is defined somewhat differently; i.e., that application of a growth factor to a neuron in one part of the brain affects growth or activity by different neurons elsewhere in the brain. While it is possible that activity in one

neuron could affect those with which it communicates[1], the present amendments to the claims make clear that the effect of the neurotrophins delivered according to the invention is on the "targeted neurons." Such neurons may, and often do, innervate other regions of the brain.

Thus, for example, uptake of a neurotrophin at the cell body of a neuron in one region of the brain may stimulate axonal growth by the neuron in another region of the brain innervated thereby. This "non-chemotropic" effect on targeted neurons is the subject of the present invention.

This phenomenon is especially well defined in the Specification at page 7, lines 1-25 (the influence of expressed growth factors on distant regions of the brain is a non-chemotropic phenomenon, possibly involving downstream activation of signaling pathways), and by:

- Example IV herein, wherein *in vivo* delivery of a growth factor expressing vector into the forebrain influenced neuronal growth by targeted neurons (at their axonal termini, remote from the delivery site) within the forebrain and extending therefrom into cortical tissue.

- The inventor's Declaration under 37 CFR 1.132 submitted herewith (originally submitted in the parent application; the "Tuszynski Declaration"), wherein *in vivo* delivery of a growth factor expressing vector into the striatum influenced neuronal growth within the substantia nigra.

[1] For the record, Applicant notes that those of skill in the art will appreciate that the practice of the invention as claimed may also stimulate growth or activity in neurons other than those to which the neurotrophin is directly delivered. Growth factor transport can occur *between cells* via intercellular transport from axonal termini. *See, e.g.,* von Bartheld, *et al., Mol.Neurobiol.,* 24:1-28 (Humana Press, 2001), of record.

III. RESPONSE TO REJECTION OF CLAIMS 1 AND 21-46 FOR LACK OF ENABLEMENT (SECTION 112, FIRST PARAGRAPH)

The Office Action appears to offer five inter-related bases for the conclusion that the claims are not enabled. First, that gene therapy in general is so unpredictable that those of ordinary skill in the art would be unable to determine whether a particular form of gene therapy is likely to perform as claimed, given differences in the fate of expressed proteins, inflammation responses to vectors, and the like. Second, that those of ordinary skill in the art would not be able to determine the metes and bounds of the claim limitation directing selection of delivery sites "within diffusion distance" of a targeted neuron.

Third, that those of ordinary skill in the art would not be able to determine areas of the brain for introduction of growth factors from which a non-chemotropic effect on treated neurons could be effected. Fourth, whether the phenomenon of non-chemotropic growth by treated neurons is sufficiently enabled. Fifth, whether only *ex vivo* practice of the invention is enabled.

Each of these contentions are traversed and addressed below in order, in Sections A-E below.

A. Efficacy Of The Claimed Method For Practicing Gene Therapy Generally.

The presently elected claims extend to *in vivo* administration of an expression vector encoding a growth factor, as is also claimed in the ancestor '058 Patent. As was confirmed during prosecution of the '058 Patent, the vectors useful in such administration can be taken up by, and expressed in, neurons in the brain. Expression can persist for many months, without untoward responses to the vector or protein, such as inflammation.

Therefore, **to the extent that the enablement rejection raises the same inquiries concerning the fate of an expression vector and expressed growth factor in brain cells that were raised in the '058 Patent**, the resolution of the issues in the '058 Patent (i.e., confirming

that transfection and expression at a sufficient level to produce a biological response can be achieved by introducing a growth factor-encoding expression vector into brain tissue) applies with equal force in the present application.

The allowance of the *in vivo* claims referenced above in the parent application indicates that the question of whether the *in vivo* practice of the invention is enabled by the disclosure has already been decided in Applicant's favor. As provided under MPEP 2124, that decision should be given "full faith and credit" with respect to the present *in vivo* method claims.

B. Placement of Delivery Sites.

However, in the present Office Action, it is asserted that the prior determination made in the '058 Patent regarding enablement of the *in vivo* practice of the invention isn't pertinent to the present claims, because they lack two limitations that are found in the '058 Patent claims: (1) that each delivery site must be no more than about 500 μM from another targeted neuron (versus, as claimed, "diffusion distance" from a targeted neuron; and (2) that each delivery site must be 10 mm from another delivery site.

1. Distance between a delivery site and a targeted neuron.

The Specification, at paragraph 0032, clearly directs those of skill in the art as to placement of each delivery site in the brain:

> "Once areas of neuronal loss (or likely neuronal loss) are identified, delivery sites are selected for stereotaxic distribution so each unit dosage of growth factor composition is delivered into the brain at the target site, or within diffusion reach of a chemotropic (concentration) gradient leading to the target site (generally, within 500 μm of a targeted neuron)." (emphasis added)

At Paragraph 0087, data from *ex vivo* practice of the invention demonstrates a diffusion distance of at least 500 μm from the delivery site of grafts placed in primate brains. However, those of ordinary skill in the art would have recognized at the time that the application was filed that the suggested "diffusion reach" of expressed growth factors in the brain could be greater than 500 μm, especially through *in vivo* (i.e., direct expression from a recombinant expression vector) introduction of growth factors.

In 1996, Mahoney and Saltzmann taught a mathematical model for determining the distance that a drug is likely to diffuse in the brain, to indicate the best location for placement of the drug molecules with respect to their desired targets (*J.Pharm.Sci.*, 85:1276-1281, 1996). The approach was applied after the invention was made to determine the distance that NGF, expressed from an rAAV vector, would diffuse for uptake in the brain (Mahoney and Saltzmann, *PNAS USA*, 8:4536-4539, 1999). Consistent with the teaching of the present Specification, NGF diffused up to 1 to 2 mm from the delivery sites (*ibid.*, see the Abstract). The diffusion rates for other molecules in the brain were previously demonstrated to be similar in various species (see, e.g., Fung, *et al.*, *Cancer.Res.*, 58:672-684, 1998) (the references cited in this paragraph are submitted herewith).

Clearly, those of ordinary skill in art were aware that therapeutic molecules introduced into the brain may diffuse from the delivery site, and were aware how to determine the diffusion distance for given molecules, including growth factors. Further, it was known that such molecules can diffuse up to about 2 mm from the delivery site, a distance greater than the 500 μm minimum distance suggested in the present Specification.

Those of ordinary skill in the art would therefore understand how placement of expression vectors within diffusion distance of a targeted neuron would result in uptake of the expressed growth factor by the targeted neuron. Applicant's teaching that expression vectors may be placed at or within diffusion reach of a targeted vector is therefore sufficient to enable those of ordinary skill in the art to practice this aspect of the invention without undue

experimentation (*In re Wands,* 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988); see also, MPEP 2164.01).

In this respect, Applicant respectfully notes that the question is not whether any experimentation by the art might be required to practice a claimed invention, but whether such experimentation is undue. The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation (See, e.g., *In re Certain Limited-Charge Cell Culture Microcarriers*, 221 USPQ 1165, 1174 (Int'l Trade Comm'n 1983), aff'd. sub nom.; *Massachusetts Institute of Technology v. A.B. Fortia*, 774 F.2d 1104, 227 USPQ 428 (Fed. Cir. 1985); *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404). Here, as discussed above, the art has the means in hand to determine diffusion distances from a delivery site for use in the invention, and actually uses those means to determine such distances for various molecules, including growth factors. Such experimentation is therefore not "undue."

Finally, for purposes of Section 112, first paragraph, a Specification need not (and preferably does not) teach that which is known in the art[2]. Therefore, as of the time the application was filed, it was unnecessary for the inventor to teach specific distances for delivery sites to be placed to ensure diffusion of the expressed growth factor to targeted neurons. It was instead sufficient to teach that placement of expression vectors within such diffusion distance could be made to practice the invention as claimed. Therefore, Applicant respectfully submits that the rejection of the present claims as not enabled with respect to the selection of a delivery site vis-à-vis its distance from a targeted neuron is incorrect, and should be withdrawn.

[2] " [A] patent application does not need to include in the specification that which is already known to and available to one of ordinary skill in the art." *Koito Mfg. Co. v. Turn-Key-Tech, LLC.*, 381 F.3d 1142, 1156 (Fed. Circ. 2004).

2. Distance between delivery sites.

With respect to the implication made in the Office Action that enablement would also require that the claims recite that each targeted neuron be no more than about 10 mm apart from one another, that limitation has not been added to the present claims, for the following reasons.

The '058 Patent claims were directed primarily to stimulation of localized *chemotropic* growth; i.e., an increase in neuronal density and activity in the region of the brain surrounding the delivery sites. In that context, the density of targeted neurons surrounding the delivery sites was a pertinent factor to consider. Therefore, the '058 Patent claims included a density limitation reciting that the targeted neurons were up to 10 mm apart.

In the present invention, however, the density of neurons adjacent to the delivery sites isn't critical to the effects claimed; i.e., growth by, or increase of activity in, a region of a targeted neuron (such as the axonal termini) in response to uptake of neurotrophin delivered to another region of the same neuron (such as the cell body). Instead, the only practical consideration with regard to the selection of a delivery site are: (a) if the site is close enough to the targeted neuron to affect it; and (b) if the targeted neuron is of interest with respect to the condition being treated. As such, it is not necessary to the practice of the invention that the distance between targeted neurons be specified.

Based on the foregoing, the claims are clearly as enabled with respect to the claimed locations of delivery sites, consistent with the determination made with respect to enablement of the claims of the parent '058 Patent. Applicant therefore submits that the prior determination of enablement in the '058 Patent should be given "full faith and credit" with respect to the present claims.

C. Selection of Delivery Sites for Therapeutic Benefit.

In addition to determining specific locations in the brain to place expression vectors encoding growth factors, the Specification also teaches that the sites should be in a region of the brain from which the claimed non-chemotropic effects on targeted neurons may be exerted.

Those of ordinary skill in the art, having the usual level of knowledge concerning the neurological structure of the brain, will have no difficulty identifying regions of the brain that (a) experience a loss of neuronal density or activity in connection with aging or impairment; and, (b) receive innervation by neurons whose loss of function is related to the effects of aging or impairment.

With that information defining the goal of treatment, artisans can readily identify the location of the soma of the targeted neurons (e.g., cholinergic neurons originating in the basal forebrain, dopaminergic neurons originating in the substantia nigra, or cortical neurons) and provide treatment according to the methods of the invention accordingly. Such anatomical and physiological information is well-known and the art, and need not be (indeed, is preferably not[3]) detailed in the Specification for the claims to be enabled. Nonetheless, particular neurons and dysfunctions of interest that are known in the art and amenable to treatment according to the invention are identified in the Specification; e.g., Alzheimer's Disease (AD) and other memory impairments (cholinergic neurons); Parkinson's Disease (PD) and other tremor impairments (dopaminergic neurons) and, in a preferred embodiment, atrophies related to aging (loss of cortical fiber density) (Specification at page 1, lines 10-26).

Therefore, Applicant respectfully submits that the claims are amply enabled by the Specification with respect to route (location) of administration, and the location of the intended effect of treatment. The rejection of the claims under Section 112, first paragraph, for lack of enablement in this regard should be withdrawn.

[3] See, note 2, supra.

D. Enablement with Respect to Teaching of Non-Chemotropic Responses Between Regions of the Brain.

The Office Action maintains the assertion that the claims do not recite that the regions of the brain affected by delivery of neurotrophin to targeted neurons elsewhere are innervated by the targeted neurons, or that the results achieved are mediated by the non-chemotropic effect of the neurotrophin on the targeted neurons. The claims have now been amended to clarify these points.

It will be appreciated that those of ordinary skill in the art would have a reasonable expectation that the invention as claimed can be practiced toward achieving the ends described in the Specification. Although the inventor was, to the best of Applicant's knowledge, the first to observe the phenomenon, it has become accepted in the art that growth factors may be transported within neuronal cells both in a retrograde direction (into cell nuclei) and an anterograde direction (to axonal termini). *See,* e.g., Conner, *et al., Proc. Natl. Acad. Sci. USA.*, 98: 1941–1946 (2001)(growth factors expressed at one site in the brain exert trophic influence over growth among neuronal populations in proximal regions of the brain); Curtis, *et al., Mol. and Cell Neurosci.*, 12:105-118 (1998) (retrograde transport of growth factors increases following injury to nerve cells); von Bartheld, *et al., Mol.Neurobiol.*, 24:1-28 (Humana Press, 2001) (anterograde transport of NGF and GDNF family growth factors and transfer thereof from axonal termini to proximal second or third order target cells); and von Bartheld, *et al., Letters to Nature*, 379:830-833 (1996)(anterograde transport and intercellular transfer of NGF family growth factors in the visual nervous system of chicks)(the references cited in this paragraph are already of record in the application).

Thus, those of ordinary skill in the art will, in view of the guidance supplied by the present disclosure, understand and agree that a neurotrophin expressed in, or taken up by, a neuron at one site may exert influence over growth of by the neuron at a significant distance from that site.

For all of the reasons expressed above and in previous amendments of record herein, Applicant respectfully submits that this basis for the enablement rejection of the claims has been overcome.

E. Enablement as to the *In Vivo* Effects of the Invention.

Lastly, the Office Action asserts that only the *ex vivo* practice of the invention is exemplified in the Specification. Applicant respectfully disagrees.

The Examiner's attention is respectfully drawn to the data provided in the Specification regarding the delivery of neurotrophins via direct introduction of a transgene-encoding AAV vector into the brain. *See*, for example, Example IV in the present Specification, wherein ***in vivo*** delivery of a growth factor expressing vector into the forebrain influenced activity and growth in the cortex (into which neurons projected from the forebrain); and in the inventor's co-pending U.S. Patent Application No. 09/730,790 (now US Patent No. 6,815,431), wherein ***in vivo*** delivery of a growth factor expressing vector into the striatum (into which neurons projected from the substantia nigra) influenced growth within the distant substantia nigra (*see also,* data set forth in the Tuszynski Declaration, submitted herewith).

It is true that the Specification also includes data relating to the *ex vivo* practice of the invention, towards proof of the principle that delivery of a neurotrophin-expressing transgene into the brain can exert a desirable impact on the growth and activity exhibited by neurons therein. However, these data do not limit the scope of the invention to its *ex vivo* practice. As stated in the Specification, "[t]hose of ordinary skill in the art will appreciate that while [certain of] the Examples illustrate an ex vivo application of the invention, the results achieved will [also] be accessible through in vivo delivery..." (Specification at paragraph 0067).

In non-human primates, Dr. Tuszynski's Declaration confirms the results of two sets of experiments using the *in vivo* technique claimed herein in aged animals, as well as art-accepted animal models of AD and PD (both non-human primates and rodents were utilized). In these experiments, expression was not only of sufficient volume (> 90% of neurons targeted were

transfected) and duration (8+ months, at last testing) to offer a therapeutic benefit to treated animals, a demonstrable improvement in motor function and cognition was confirmed. See, e.g., data presented in Tuszynski Declaration, at 3, 6, 12, 14-21 and 25-29.

Expression in these animals persisted throughout the test period (in excess of 8 months for several animal sets). Although expression may decline over time, the expression which is achieved is sufficient to treat, and possibly even reverse, the cognitive and motor function impairment observed in the test animals. Tuszynski Declaration, at 3. Moreover, these results were achieved without detectable inflammation in the brain. Tuszynski Declaration at 4, 6 and 12.

In human clinical trials, responses to expression of exogenous neurotrophin introduced into the brain according to the invention have been remarkable. For example, the rate of progression of AD in the first patient treated (with the *ex vivo* approach) is estimated to have been slowed by upwards of 51%, a heretofore unprecedented result in treatment of AD (see Tuszynski, *et al., Nat. Medicine,* 11:551-555, 2005, at 553, first column, enclosed). The *Nature Medicine* paper also reports promising results from a trial for treating PD using the invention, at 553, second column.

Human clinical trials of the *in vivo* practice of the invention are also enjoying promising, if preliminary, results. These results offer hope that the beneficial effects produced in patients participating in the *ex vivo* trials may be realized for a longer period of time among patients treated with the *in vivo* approach, which does not rely on the longevity of exogenous cell grafts (see, the *Chicago Tribune* article dated August 16, 2005, enclosed).

The invention therefore represents a truly extraordinary achievement in the treatment of human disease. The results of the trials to date confirm that the invention, as disclosed and claimed, stimulates neuronal growth and activity as predicted. The therapeutic benefits of the invention may therefore not only mitigate the effects of diseases such as AD on the brain, but

also offers a chance to improve the quality of life for sufferers to an extent that could, for example, delay the time when skilled nursing care becomes necessary.

In conclusion, the present disclosure establishes that transfection and persistent expression in brain cells to produce the *in vivo* effects to which the invention is directed can be achieved. Therefore, the enablement rejection has been fully addressed and overcome in this respect, and should be withdrawn.

For all of the foregoing reasons, Applicant submits that the claims as amended are fully enabled by the Specification. Therefore, reconsideration and withdrawal of the rejection of the claims under Section 112, first paragraph is respectfully requested.

IV. RESPONSE TO OBJECTION TO PRIORITY CLAIM

In the Office Action, the refusal of Applicant's priority claim to Serial No 09/060,543, now U.S. Patent No. 6,451,306 (the '306 Patent) is continued. In particular, the Examiner queries what was referred to by the "'053 Application" in the previous amendment.

Applicant apologizes for the confusion caused by the typographical error in the prior Amendment. The reference to the "'053 Application" should have been to the "'543 Application," now U.S. Patent No. 6,451,306. In that respect, Applicant renews his assertion that he is entitled to the priority of the '543 Application ('306 Patent) for all claimed subject matter common to it and the present application, under 35 USC Section 120.

Under Section 120, it is clear that, in a continuation-in-part application "matter disclosed in the parent application is entitled to the benefit of the filing date of the parent application." *Waldemar Link, GmbH & Co. v. Osteonics Corp.*, 32 F.3d 556, 558, 31 USPQ2d 1855, 1857 (Fed.Cir.1994). The benefit of the filing date of an earlier application is accorded for all common subject matter if there is at least one common inventor between the applications, the

CIP was filed while the parent application was still pending, and the CIP contains a reference back to the parent application. *See*, MPEP 201.08.

All of these conditions are met in the present application, which contains subject matter common to the disclosure of the '543 Application ('306 Patent), as set forth in Applicant's Amendment of June 21, 2004. As such, it is respectfully submitted that the priority claim for *subject matter common to the present application and the '543 Application ('306 Patent)* ancestor disclosure should be granted.

CONCLUSION

Applicant believes that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested.

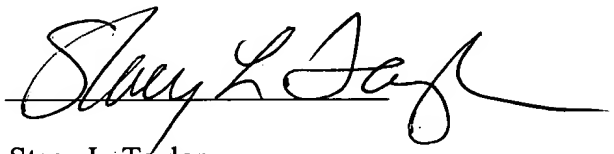
The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 50-0872. Should no proper payment be enclosed herewith, as by a check being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 50-0872.

If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant hereby petitions for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 50-0872.

Respectfully submitted,

Date October 11, 2005

By 

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Enclosures: Clean copy of amended claims